## REMARKS

### Status of the Claims

Claims 1-11 are pending in the present application. Claims 10-11 are withdrawn as directed to a non-elected invention. Claims 1, 6, 8, and 10 are amended.

Claims 1 and 10 are amended to specify "wherein the transposon segment is integrated by transposition into the cellular nucleic acid of said target cell and the integration is mediated by MuA only." Support for amended claims 1 and 10 is found throughout the application as originally filed including on page 4, lines 12-14, which states: "[i]n the simplest case, the MuA transposase protein and a short 50 bp Mu right-end (R-end) fragment are the only macromolecular components required for transposition complex assembly and function...." Claim 6 is amended for consistency with claim 1. Claim 8 is amended to specify "a fraction comprising Mu transposition complexes is concentrated and desalted from Mu transposition complex assembly reactions and is delivered into the target cell." Support for amended claim 8 is found, for example, on page 9, lines 21-22 in the originally filed application. No new matter is added by way of this amendment. Reconsideration is respectfully requested.

### Request for Rejoinder

Applicants request that at least claim 10 be rejoined with claims 1-9. Applicants submit that at least claims 1-10 relate to a single general inventive concept and satisfy the unity of invention requirement since the claims include a technical feature that makes a contribution over the art. In particular, the claims describe an *in vitro* assembled Mu transposition complex that comprises (i) MuA transposases and (ii) a transposon segment that comprises a pair of Mu end sequences recognized and bound by MuA transposase and an insert sequence between said Mu end sequences, wherein the transposon segment is integrated by transposition into the cellular nucleic acid of said target cell and the integration is mediated by MuA only. In view of this special technical feature, withdrawal of the restriction requirement and rejoinder of the claims is respectfully requested.

### Issues under 35 U.S.C. § 102(b)

Claims 1-4 and 7-9 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Publication No. 2002/0094575 to Suzuki, ("Suzuki"), *see* Office Action, pages 2-3. According to the Examiner, Suzuki describes all of the elements of the claimed method. The Examiner further states that Suzuki teaches that the complexes described therein may be used in mammals. Applicants respectfully traverse.

*The claims are not anticipated by Suzuki*

As noted above, independent amended claim 1 is directed to a method for incorporating nucleic acid segments into cellular nucleic acid of an isolated mammalian target cell, the method comprising the step of: delivering into the mammalian target cell an *in vitro* assembled Mu transposition complex that comprises (i) MuA transposases and (ii) a transposon segment that comprises a pair of Mu end sequences recognised and bound by MuA transposase and an insert sequence between said Mu end sequences, wherein the transposon segment is integrated by transposition into the cellular nucleic acid of said target cell and the integration is mediated by MuA only.

In contrast to amended claim 1, Suzuki indicates that the use of MuB is essential for the method described therein, particularly for target site selection, *see* abstract of Suzuki. Accordingly, the MuB-assisted Mu transposition, as disclosed in Suzuki, is not encompassed by the claimed method, which specifies that "the integration is mediated by MuA only." Accordingly, the claims are not anticipated by Suzuki. Withdrawal of the rejection is respectfully requested.

*The claims are not rendered obvious by Suzuki*

Applicants further submit that the instant claims are not obvious in view of Suzuki. As noted above, Suzuki indicates that the use of MuB is essential for the method described therein, particularly for target site selection. In addition, a main technical difference between the claimed methods and Suzuki is that mammalian cells, instead of plant cells, are transformed in the instantly claimed methods. Applicants submit that at the time of the invention, an ordinary artisan could not have reasonably predicted that mammalian cells could have been transformed by transposition complexes. In fact, at the time the invention was made, the prior art including Suzuki contained no evidence of successful transformation of mammalian cells by transposition

complexes, only speculative plans were disclosed suggesting the possibility to do so. Accordingly, the examples of Suzuki disclose transformation with plant cells only.

Applicants further submit that, even if a person skilled in the art could have been motivated by the suggestions made in the prior art (*e.g.* by Suzuki) to try the transformation of a mammalian cell with a transposition complex, it is clear that in view of Schagen *et al.*, *Nucleic Acids Research*, 2000, 28:1-7, ("Schagen"), of record, she/he would have never chosen a MuA transposition based system for such an experiment. Schagen discloses that no sign of *bona fide* Mu transposition was detected in the transformed mammalian cells when a MuA and MuB based transposition system was used with said cells, *see* the abstract and the last paragraph of discussion in Schagen. Therefore, a MuA transposition based system would have been the least expected of such systems to be active inside mammalian cells.

As further evidence of the unpredictability of the art, Applicants submit herewith the April 8, 2004, Office Action, which issued in U.S. Publication No. 2002/0094575 to Suzuki. This Office Action discusses the unpredictability of Mu functioning in a variety of host cells. In view of the foregoing, the claims are not rendered obvious by Suzuki.

**Issues under 35 U.S.C. § 103(a)**

Claims 5 and 6 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Suzuki, *see* Office Action, pages 3-4. The Examiner states that Suzuki teaches all of the elements of the instant claims except for human or mouse cells. According to the Examiner, the selection of human or mouse cells would have been obvious to one of ordinary skill in the art at the time of the invention since such cells were widely used mammalian cells.

As noted above, Suzuki fails to teach all of the elements of the instant claims. In particular, Suzuki fails to describe that the integration is mediated by MuA only. In addition, as described above and as evidenced in Schagen and the enclosed Office Action, which issued in Suzuki, an ordinary artisan could not have reasonably expected that the MuA transposition based system described in the present claims would have been active inside mammalian cells. Accordingly, the claims are not rendered obvious by Suzuki. Withdrawal of the rejection is respectfully requested.

**Issues Under 35 U.S.C. § 112, second paragraph**

Claims 6 and 8 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly lacking clarity, *see* Office Action, pages 4-5.

Applicants submit that in view of the amendments to claims 6 and 8, the claims are not indefinite. Accordingly, withdrawal of the rejection is respectfully requested.

## CONCLUSION

In view of the amendments, remarks and evidence submitted herewith, Applicants believe the instant application is in condition for allowance. Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Ph.D., Registration No. 46,046, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: NOV 22 2010

Respectfully submitted,

By _____
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**Attachment**

A7

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/951,829 | 09/13/2001 | Hideki Suzuki | 35718/238818 (5718-124) | 3263 |

29122 7590 04/08/2004

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| EXAMINER | |
|---|---|
| HELMER, GEORGIA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1638 | |

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/951,829 | SUZUKI, HIDEKI | |
| | Examiner | Art Unit | |
| | Georgia L. Helmer | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 September 2004 and 17 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12 and 16-22* is/are pending in the application.

4a) Of the above claim(s) *12,18 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,16,17,19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Restriction election & Status of the Claims*

1. The Office acknowledges the receipt of Applicant's Response, filed 22 September 2003. Applicant sequence CRF submitted 17 December 2003 has been entered. Claims 1-12 and 16-22 are pending. Claim 12 is withdrawn as drawn to a nonelected invention. Claims 13-15 are cancelled. New claims 16-22 have been added. Newly submitted claims 18 and 20 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 18 and 20 are drawn to a method comprising a Mu transposable cassette flanked by restriction enzyme sites that have undergone double stranded cleavage is a distinct invention from Group I requiring different components, different steps and resulting in distinct products.

2. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 18 and 20 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims examined are 1-11, 16, 17, 19, 21,and 22.

4. This application contains claim 12, drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

**5.** This action is made FINAL necessitated by Applicant's amendment.

6. All rejections not addressed below have been withdrawn.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Specification***

8. Applicant's update of the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification is noted. US filed applications in the specification update is also noted.

Applicant's removal of embedded hyperlink and/or other form of browser-executable code is noted.

***Information Disclosure Statement***

9. It is noted that Applicant has included reference articles with this Response. However, a proper submission of references must include a filled-out PTO 1449 for consideration by the Office.

***Claim Rejections - 35 USC § 112-second***

10. Claims 11 and all claims dependent thereon are rejected under 112-2$^{nd}$ because the dependency of claim 11 on claim 7 is improper as claim 11 is drawn to a bacterial cell and claim 7 is drawn to a plant cell.

***Claim Rejections - 35 USC § 112-1-enablement***

11. Claims 1-11, 16, 17, 19, 21,and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record, which are repeated in part below. To the extent that this is a new rejection, it is necessitated by Applicant's amendment.

The claims are drawn to a method of stably integrating a nucleotide sequence of interest into the genome of a host cell, said method comprising: (a) providing a MuB protein to cell, and (b) providing said cell of with an active cleaved donor complex comprising a Mu transposable cassette having a first end and a second end and comprising said nucleotide of interest, wherein a single-stranded nick has been introduced at said first end and said second end of said Mu transposable cassette, whereby said Mu transposable cassette comprising said nucleotide sequence of interest is stably integration into the genome of said host cell.

*The state of the art and the predictability or lack thereof in the art.* The state of the art is such that one skilled in the art can readily make DNA constructs and introduce them into cells. However, it is unpredictable whether such sequences, upon introduction, will be transformed into the genome, and if transformation does occur, whether such transformation will be stable. Successful transformation with Mu requires host factors, including HU (Craigie, Cell, 85, pages 137-140, 1996, page 137, 1st column) as well as cis DNA sequences (IAS) (Craigie, Cell, 85, pages 137-140, 1996,

page 137, 2nd column). It is unpredictable that all cells of any host, would provide the required host factor(s) so as to allow the Mu derivative DNA to function as desired. Rather, since Mu is an E.coli bacteriophage (Toussaint et al, Phage Mu: Transposition as a Life -Style, pages 105-158, especially p. 108, in Mobile Genetic Elements, 1983, ed. Shapiro, J, Academic Press, NY), it is predicted that MU would function predictably in E.coli, and prokaryotic hosts, but that Mu function in eukaryotic hosts would be unpredictable.

Applicant traverses saying primarily (Response, p. 13) while HU if present may be involved in the formation of the stable synaptic complex, it is not necessary under certain conditions, as discussed in the specification. Applicant further states, that HU if present is involved in the formation of the stable synaptic complex, which is a precursor to the cleaved donor complex, and that the active cleaved donor complex of the claims can be assembled in vitro and then transformed into the host cells of interest. Applicant's traversal is unpersuasive. Applicant's arguments are not commensurate in scope with the claims. With the exception of Claim 19, none of the claims recite a cleaved donor complex produced in vitro.

Simple heterologous expression constructs in any given host system are clearly structurally different from heterologous expression constructs in other host systems, including mammalian, yeast and bacterial systems. Required are different promoters, enhancers, codon optimization, termination regions, and other regulatory regions. In the expression of heterologous constructs, the constructs must be recognized by the cell

machinery. Otherwise, the construct would be degraded or removed from the cell. No construct to date is universally recognized in all cells. One of skill in the art would expect a heterologous expression system constructed for prokaryotic cells to differ from one functional in eukaryotic cells.

*The state of the art and the predictability of the art*: Plant transformation procedures employing plant tissue culture protocols are unpredictable. "Plant transformation is an art because of the unique culture conditions required for each crop species. To accommodate a genotype or species that has not been manipulated in culture previously, one must either adapt an established protocol or create a new one", (Hansen et. al., 1999, Trends in plant Science, vol 4, pages 226-231, see page 230). Furthermore, the success of specific cells for the claimed transformation the specific cell used as host for the claimed transformation are unpredictable as indicated by Tisserant, B in Plant cell culture: a practical approach. 1985, pages 79-105, see especially Table I, page 82, and Table 4, pages 85-90.

*Guidance and working examples*: Applicant claims a method of transformation and expression for any cell of any and all cells, including bacteria, fungi, algae, all animals, which includes mammalian cells. Further claims are drawn to plant cells, monocot cells, cells of maize, wheat sorghum, rice barley oats, and rye, dicot plant cells, and bacterial cells. Applicant claims all monocots, including the taxonomically divergent species palm, orchid, iris, asparagus, onion and corn. Applicant claims any plant cell from any explant source.

Applicant's specification includes only prophetic examples. These examples are of plant cells—immature zygotic maize embryos from ears (specification, p. 46) and soybean somatic embryos from cotyledon explants (specification, p.49). Applicant has working examples of no cells of any host or any explant of any plant tissue. While working examples are not required, Applicant must provide sufficient guidance to address the issues discussed above. Without such guidance, the experimentation required would not be routine, but would be undue.

Applicant traverses saying primarily that (Response, p.14) amended claim 1 specifies that the claimed method comprises providing MuB proteins within said cell and providing said cell with active cleaved donor complex comprising a Mu transposable cassette wherein a single stranded nick has been introduced at each end of said Mu transposable cassette. Guidance for making and using embodiments having these limitations can be found in the specification, pages 8-10, 14, 15 and 26. Applicant's traversal is unpersuasive .

Claim 1 is drawn to a method, having the recited steps a and b, "whereby the Mu transposable cassette ....is stably integrated into the genome of said host cell". Applicant has not a single working example of such stable integration into the genome of any host, prokaryotic or eukaryotic. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of possibilities other than by random trial and error, which is excessive experimentation

and an undue burden. Without further guidance, one of skill in the art would be required to do many experiments involving a myriad of combinations. This would impose a burden on the skilled artesian, without a reasonable expectation of success.

Applicant traverses saying primarily (Response, p. 14) that work by others supports the enablement of Applicant's claimed invention, citing Lamberg et. al., App. Env. Microbiol. 68:705-712 (2002). Applicant's traversal has been considered and is unpersuasive. The patent application must be enabled as of the date of filing. The reference of Lamberg was published February 2002. Applicant's priority date appears to be 14 September 2000. Therefore the post-filing date reference of Lamberg et. al. cannot be used to support enablement as of the date of filing.

Applicant traverses saying primarily that Larocca (1999) FASEB J. vol 13, pages 7272-734, (appendix E) showed that gene transfer into eukaryotic cells can be accomplished using the genetic machinery of filamentous phages. Applicant's traversal is unpersuasive. Larocca teaches transduction of a GFP reporter gene into COS-1 mammalian tissue culture cells using a modified M13 filamentous phage. Mammalian cells are notably different from plant cells in that mammalian cells do not have cell walls. Plant cell walls provide a very clear barrier to biological penetration or permeation. The work of Larocca employs phage transduction—a biological transfer system. The work of Larocca is scientifically interesting but is not relevant to the claimed invention.

**Remarks**

12. SEQ ID NO: 3, 4 and 5 are known in the prior art.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 571-272-0976. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Georgia Helmer PhD
Patent Examiner
Art Group 1638
April 5, 2004

ELIZABETH F. McELWAIN
PRIMARY EXAMINER
GROUP 1800